REMARKS

Status of claims:

Upon entry of this amendment, claims 21-52 will be pending, claims 1-20 having been newly canceled without prejudice and new claims 21-52 added. It is believed that all of the new claims are within the elected restriction group. Support for new claims 21, 27, 34, 39, and 46 can be found in original claims 1 and 2, and in the substitute specification at page 1, lines 10-13; page 7, lines 33-35; and page 8, lines 1-9. Support for new claims 22, 30, 35, and 42 can be found in the substitute specification at page 8, lines 12-13. Support for new claims 23, 28 and 40 can be found in the substitute specification at page 10, lines 23-28. Support for new claims 24, 31, 36, and 43 can be found in the substitute specification at page 8, lines 18-27. Support for new claims 25, 32, 37, and 44 can be found in original claims 3 and 4. Support for new claims 26, 33, 38, and 45 can be found in original claim 9. Support for new claims 29 and 41 can be found in the substitute specification at page 10, lines 5-22. Support for new claims 47-52 can be found in original claims 6, 11-13, 15, and 19. No new matter has been added. Entry of the above amendment and allowance of all pending claims in view of the remarks in this Response are respectfully requested.

Amendments to Specification:

The specification has been amended to ensure that the nucleotide positions of several sequences within in SEQ ID NO:6 are accurately recited in reference to SEQ ID NO:6. The correct positions are apparent from review of SEQ ID NO:6. No new matter has been added.

Information Disclosure Statements

Applicants thank the Examiner for considering the previously-filed Information Disclosure Statements. A new Information Disclosure Statement citing additional documents is enclosed. The Office Action at page 4 notes that a number of references are listed in the specification, and comments that such a list is not a proper information disclosure statement. Applicants note for the record that each of the references listed in the specification at pages 1-3

has already been cited in a proper Information Disclosure Statement (and initialed by the Examiner) in the present case.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-4, 6-8, 10-13, 15, 17, and 19 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite because, according to the Examiner, the term "WT-1" is not clearly defined. These claims have been canceled and replaced with new claims that use the term "Wilm's tumor gene" instead of "WT-1". As this is the substitution suggested by the Examiner, Applicants believe that this renders the rejection moot.

Rejection under 35 U.S.C. § 102(b)

The Examiner rejected claims 1, 2, 6-8, 10-13, 15, 17, and 19 under 35 U.S.C. § 102(b) for allegedly being anticipated by Hübinger et al (*see*, Office Action, page 6).

As a preliminary matter, Applicants note that claims 1, 2, 6-8, 10-13, 15, 17, and 19 have been canceled. Therefore, the rejection as to those claims is moot. This rejection is addressed as it may relate to the newly added claims.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

Hübinger et al. is cited for its disclosure of anti-WT1 ribozymes and anti-WT1 ribozyme vectors used to inhibit WT-1 gene expression and proliferation in leukemia cells in culture (*see*, Office Action, pages 7-8). Applicants note that the newly added claims are limited to siRNAs, DNAs transcribed into the siRNAs, and vectors containing those DNAs. The claims do not encompass ribozymes or ribozyme vectors such as those disclosed in Hübinger et al. Therefore, Hübinger et al. does not anticipate Applicants' claimed invention.

Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 103(a)

The Office Action rejected claims 1-4, 6-8, 10-13, 15, 17, and 19 under 35 U.S.C. § 103(a) for allegedly being obvious over Yamagami et al. in view of Murata et al. and Hammond et al (*see*, Office Action, pages 10-17). These claims have been canceled, rendering the rejection moot as to them. Insofar as the rejection may be applied to the new claims, Applicants traverse.

The Office Action at page 13 alleges that Yamagami et al. disclose antisense oligonucleotides complementary to a WT1 gene transcript used to inhibit WT1 expression in leukemia cell lines and to inhibit proliferation and cell growth in leukemia cell lines. The Office Action acknowledges at page 15 that "Yamagami et al. do not teach that the agent is double-stranded. Yamagami et al. also do not teach that the double-stranded RNA comprises an RNA complementary to a 17AA site of WT1 gene transcript." According to the Office Action, Murata et al. teach that a splicing variant of WT1, WT1-17AA, induces G1 arrest and apoptosis in leukemia cells, and "Hammond et al. teach that antisense and RNA interference are two methods of silencing expression of a gene and that RNA interference possesses characteristics that make it superior to antisense." The Office Action alleges that it would have been *prime facie* obvious at the time of the invention to one of ordinary skill in the art to combine the teachings and motivation of Yamagami et al. and Hammond et al. to make a cell growth-suppressing agent comprising a double-strand RNA comprising an RNA complementary to a WT1 gene transcript as an active agent. The Office Action also alleges that it would have been *prime facie* obvious at the time of the invention to one of ordinary skill in the art to combine the teachings and motivation of Yamagami et al. and Murata et al. to have the double-stranded RNA comprise an RNA complementary to a 17AA site of WT1 gene transcript (*see*, Office Action, page 16). Applicants respectfully disagree for reasons that are elaborated below.

As noted by Murata et al. at page 41, left column; by Yamagami at page 2881, right column, first paragraph; and by the present specification at page 1, lines 10-14, there are four known splice variants of the WT1 gene. One of the splice variants contains both the 17AA site (in exon 5 of the WT1 gene, according to www.ncbi.nlm.nih.gov/nucleotide/65508003) and the

KTS site (in exon 9); one contains neither the 17AA site nor the KTS site, one contains the 17AA site but not the KTS site, and the fourth contains the KTS site but not the 17AA site. Murata et al. explains that the four splice variants possess different activities attributable to the presence or absence of the 17AA site and the KTS site (see page 41, first column).

Yamagami et al. designed their antisense oligomers to target 20 different selected sites in the WT1 coding and noncoding sequences (see Fig. 1 on page 2879). As can be seen in Fig. 1, all of the targeted sites were outside of exons 5 and 9, so outside of the 17AA and KTS sites. This ensured that every antisense oligomer tested by Yamagami et al. would target sequence common to all four splice variants. Yamagami et al. found that four of these antisense oligomers were effective at inhibiting growth of leukemia cells (see, e.g., Figs. 1 and 2). Yamagami et al. then examined whether the cell growth-inhibiting effect of these oligomers would be reduced by recombinant overexpression of just one of the four WT1 splice variants in the cells. They found that recombinant overexpression of one of the splice variants (the "full-sized WT1 cDNA") only partially overcame the growth-inhibiting effects of each antisense oligomer, and speculated at page 2881, right column, that this inability to completely restore cell growth by overexpression of the WT1 gene might be because each antisense oligomer was targeting all four splice variants, rather than only the one that was recombinantly overexpressed. This suggests that the WT1-dependent growth of the leukemia cells used in the experiments was attributable to the endogenous expression of at least two and perhaps all four of the WT1 splice variants in the cells. It further suggests that, if maximal inhibition of WT1-dependent cell growth is desired, the best antisense strategy would utilize an antisense oligomer that targets all four splice variants, such as any of the antisense oligomers studied by Yamagami et al.. Nothing in Yamagami et al. would suggest any reason to deliberately select an antisense target that would affect at most only two of the four splice variants. In fact, Applicants see nothing in Yamagami et al. that would suggest selecting an antisense sequence other than one of the four Yamagami et al. actually showed to be effective. Given the failure rate of the antisense oligomers tested by Yamagami et al. (only 4 of 20 proved to be capable of significantly inhibiting cell growth), it is not at all predictable that targeting an antisense oligomer to an entirely different region of the gene would

be effective. It is even less predictable that targeting that region with an siRNA instead of an antisense oligomer would work.

The Office Action cites Murata et al. as providing the motivation for targeting the 17AA site in particular. According to the Office Action at page 17, "One of ordinary skill in the art would have expected success at having the double-stranded RNA comprise an RNA complementary to a 17AA site of WT1 gene transcript since Murata et al. taught the successful use and design of such a site for antisense inhibition." This statement in the Office Action is not understood. Applicants do not see any mention in Murata et al. of antisense inhibition at the 17AA site, much less "successful use and design of such a site for antisense inhibition." The Examiner is asked to point to where in Murata et al. she sees that teaching so that Applicants can respond appropriately. The only mention of antisense oligonucleotides that Applicants find in Murata et al. is in the Introduction section on page 41, right column, where the Yamagami et al. paper is cited. As noted above, Yamagami et al. tested 20 different antisense target sites in the WT1 gene, not one of which was in the 17AA site.

Rather than motivate one of ordinary skill to select the 17AA site in particular for targeting with antisense or siRNA, as urged by the Examiner, in fact Murata et al. *taught away* from doing so. Murata et al. showed that recombinant expression of one of the WT1 splice variants containing the 17AA site in leukemia cells inhibited cell growth and induced apoptotic cell death. See, e.g., page 41, right column, end of first paragraph, and Fig. 2. One of ordinary skill would logically conclude that expression of this particular splice variant ($17AA^+$, KTS^-) is likely to be beneficial in controlling cell growth, and that reducing its level of expression by use of antisense or siRNA that targets the 17AA site would be dangerously counterproductive. Recombinant expression of the other $17AA^+$ splice variant ($17AA^+$, KTS^+) had no effect on cell growth in Murata et al.'s cells (see Fig. 2), so reducing this splice variant' level of expression would appear to be pointless.

Thus, neither Yamagami et al. nor Murata et al. supplies a motivation to target the 17AA site of the WT1 gene with antisense or siRNA. In fact, as explained above, each of these references supplies a reason to avoid targeting the 17AA site in particular. Further, nothing in

the art would give a reasonable expectation that targeting the 17AA site would successfully inhibit growth of cells. Hammond et al. does not address the WT1 gene at all, much less its various isoforms, so does not make up for the deficiencies of Yamagami et al. and Murata et al. It is submitted that these references, taken alone or in combination, do not establish a prima facie case of obviousness. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103(a).

CONCLUSION

Applicants submit that the claims are in condition for allowance and respectfully request that a Notice of Allowance be timely issued.

The fee for excess claims in the total amount of $624 is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney docket No.: 14875-0168US1.

Respectfully submitted,

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